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Abstract: **OBJECTIVE:** Dilutional hyponatremia is a serious adverse effect of desmopressin, a vasopressin analog that is widely prescribed to manage monosymptomatic enuresis. The presentation of hyponatremia, largely related to cerebral dysfunction, can include severe signs like altered mental status and seizures. **METHODS:** We reviewed the literature dealing with altered mental status or seizures in enuretic subjects on desmopressin. The retained publications included patients who were described individually, revealing data on mode of administration, further identifiable factors predisposing to hyponatremia, presentation and clinical course. **RESULTS:** We found 54 cases of hyponatremia secondary to desmopressin treatment presenting with altered mental status or seizures. In most cases the complication developed 14 days or less after starting desmopressin. An intranasal formulation had been used in 47 patients. Excess fluid intake was documented as a contributing factor in at least 22 cases. In 6 cases severe signs of hyponatremia developed in the context of intercurrent illnesses. **CONCLUSION:** Altered mental status or seizures are very rare but recognized complications of desmopressin in enuresis. This complication mostly develops in subjects managed with the intranasal formulation 14 days or less after starting the medication, following excess fluid intake and during intercurrent illnesses.

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Severe signs of hyponatremia secondary to desmopressin treatment for enuresis: a systematic review

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Abstract

Objective: Dilutional hyponatremia is a serious adverse effect of desmopressin, a vasopressin analog that is widely prescribed to manage enuresis. The presentation of hyponatremia, largely related to cerebral dysfunction, can include severe signs like altered mental status and seizures.

Methods: We reviewed the literature dealing with altered mental status or seizures in enuretic subjects on desmopressin. The retained publications included patients who were described individually, revealing data on mode of administration, further identifiable factors predisposing to hyponatremia, presentation and clinical course.

Results: We found 54 cases of hyponatremia secondary to desmopressin treatment presenting with altered mental status or seizures. In most cases the complication developed 14 days or less after starting desmopressin. An intranasal formulation had been used in 47 patients. Excess fluid intake was documented as a contributing factor in at least 22 cases. In 6 cases severe signs of hyponatremia developed in the context of intercurrent illnesses.

Conclusion: Altered mental status or seizures are very rare but recognized complications of desmopressin in enuresis. This complication mostly develops in subjects managed with the intranasal formulation 14 days or less after starting the medication, following excess fluid intake and during intercurrent illnesses.

Keywords Altered mental status – Convulsions – Desmopressin – Enuresis

- Hyponatremia

Introduction

Enuresis, the involuntary release of urine by night in the absence of defects of the nervous system or urinary tract, is common among school-age children and adolescents [1-4]. For this condition the vasopressin analog desmopressin acetate (1-deamino-8-D-arginine vasopressin, often abbreviated DDAVP) is widely prescribed and well tolerated. The dose of desmopressin, which is administered either intranasally (since approximately 1980) or orally (since approximately 1990) 30-60 minutes before bedtime, is titrated to best effect and the antienuretic efficacy is seen without delay once the effect is reached [1-4].

The most serious adverse effect of desmopressin is dilutional hyponatremia. To prevent hyponatremia, fluid intake is limited from one hour before to eight hours after administration of desmopressin [1-4]. Furthermore, desmopressin is interrupted during intercurrent illnesses that predispose to fluid or electrolyte imbalance such as fever, vomiting or diarrhea [1-4]. The manifestations of hyponatremia are largely related to dysfunction of the central nervous system and are more conspicuous when the decrease in the sodium concentration is large or rapid. Headache, nausea or vomiting are the most common presentation. More rarely, severe signs like lethargy, restlessness, disorientation and epileptic seizures can be observed.

The aim of the present report is to systematically review the cases of altered mental status or epileptic seizures that result from dilutional hyponatremia associated with the use of desmopressin in subjects affected by enuresis.

Methods

Between August and October 2012 we performed a thorough computer-based search of the terms “desmopressin hyponatr[a]emia enuresis”, “DDAVP

hyponatr[a]emia enuresis”, “desmopressin hyponatr[a]emia bedwetting” and “DDAVP hyponatr[a]emia bedwetting” in the U.S. National Library of Medicine database. For this purpose we used the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [5]. We retained for the final analysis exclusively reports available as a full-length article or as a letter, which included individually described cases of epileptic seizures or altered mental status caused by hyponatremia associated with the use of desmopressin in enuretic subjects. Reports commenting the aforementioned cases and studies addressing the possible mechanisms underlying the tendency towards severe signs of hyponatremia were also retained. Pertinent secondary references found in the articles were also considered. Reports published in languages other than English, French, German, Italian, Portuguese, or Spanish were excluded. If the same case was present in different publications, we retained exclusively the most complete description. From each report dealing with severe signs of hyponatremia in subjects with enuresis managed with desmopressin, two of us (BL and MGB) independently excerpted data on gender; age; dosage and mode of administration of desmopressin; further identifiable factors predisposing to hyponatremia; clinical presentation; blood sodium concentration; and clinical course.

Descriptive statistics are presented as median and interquartile range or as relative frequency, as appropriate. The two-sided Wilcoxon-Mann-Whitney test for two independent samples and the two-sided Fisher exact test were performed for analysis. Significance was assumed when $P < 0.05$.

Search results

The flowchart of the literature search process (figure 1) indicates that the initial search revealed 164 publications, of which 115 remained after

excluding duplicates (ie, publications found with two or more search terms). Eighty of them were reviewed in detail and 31 were retained for the final analysis. Five pertinent reports were found in the references of the mentioned 31 reports. Hence, a total of 36 reports were included in the final analysis [6-40]: 31 in English [6-36] and 5 in French [37-41]. They had been reported from the following countries: United States of America (N=7), Great Britain (N=6), France (N=5), Belgium (N=3), Canada (N=3), Denmark (N=2), Germany (N=2), Switzerland (N=2), Czech Republic (N=1), Finland (N=1), India (N=1), Ireland (N=1), Israel (N=1), and South Africa (N=1).

Results

Patients with severe signs of hyponatremia

Fifty-four cases of hyponatremia secondary to desmopressin treatment presenting with severe signs were found in 31 reports [6-29, 37-41]. In addition to desmopressin, three patients were on long-term medication with oxybutynin and two with imipramine. Severe signs of hyponatremia can occur at any time after starting medication with desmopressin. In exactly half of the cases where this could be determined, however, severe signs of hyponatremia developed within 14 days. It is true, however, that in 10 percent of the cases severe signs of hyponatremia occurred one year or more after starting desmopressin.

The age of the 54 subjects ranged from 2.0 to 37, median 9.0 years with a male to female ratio of 1.71 (table 1). At least 31 patients (57 percent) reported headache, nausea or vomiting before the onset of severe signs of hyponatremia. As compared with 8 patients presenting exclusively with altered mental status, 46 patients presenting with epileptic seizures had a significantly lower blood sodium concentration ($P<0.01$) and were more frequently male ($P<0.05$). An oral formulation (either a tablet or a lyophilizate) had been used in 7 cases and the intranasal formulation (either

droplets or a spray) had been used in the remaining 47 patients. Excess fluid intake was documented as a contributing factor in at least 22 of the 54 cases (41 percent). Three further subjects (6 percent) were concurrently managed with desmopressin and oxybutynin. It is tempting to assume an excess fluid intake in these patients due to oxybutynin-induced dry mouth mucosa. Finally, in 6 cases (11 percent) severe signs of hyponatremia developed in the context of intercurrent illnesses that predispose to fluid or electrolyte imbalance (large fluid intake to maintain hydration is generally advised in these common conditions). Patients with severe signs of hyponatremia on treatment with nasal desmopressin and those on oral desmopressin did not significantly (table 2) differ with respect to median age, male to female ratio and contributing factors (either excess fluid intake or an intercurrent illness). However, blood sodium was lower on average by 8 mmol/L ($P<0.02$) in patients treated with an intranasal desmopressin formulation.

No long-term sequelae were reported with the exception of the case of a 27-year-old Irish man, an occasional heavy binge drinker treated for 8 years with desmopressin nasal spray for enuresis [18]. After consuming alcohol, he developed seizures and subsequently fell off a chair injuring his head. He was found to be deeply comatose with a Glasgow Coma Scale score of 4/15 and with a blood sodium level of 116 mmol/L. Imaging studies disclosed a left fronto-temporal contusion with mass effect and a small subdural hematoma. Despite careful correction of low sodium and appropriate management of head injury, he developed severe cerebral edema and died [18].

Metabolism of desmopressin in subjects with tendency towards hyponatremia

A Belgian group observed that some enuretic subjects managed with intranasal desmopressin delay their first morning voiding until late in the afternoon and sometimes present signs possibly consistent with hyponatremia like headache, nausea or vomiting. As a consequence, these authors suspected

the existence of a prolonged desmopressin bioactivity [30]. In a group of pediatric patients on intranasal desmopressin for enuresis, a prolonged maximal urinary concentration capacity and a delayed restoration of daytime diluting capacity were noted, thereby supporting the hypothesis of prolonged desmopressin bioactivity [30]. The intriguing report, which did not address the bioactivity of desmopressin following oral administration, has been widely debated [31-33, 35].

Discussion

Vasopressin regulates blood sodium concentration through the control of water excretion by the kidney and it exerts an antidiuretic effect that is mediated by renal receptors [42]. Vasopressin also has a vasopressor effect that is mediated by vascular receptors [42]. Desmopressin acetate is a selective renal receptor agonist and it has no effect on vascular receptor: as such, the drug retains the antidiuretic properties of vasopressin but it avoids vasopressor effects. The most important current indication for desmopressin, which was originally developed for the management of central diabetes insipidus, is enuresis. For enuresis, desmopressin is available as nasal spray (administered in doses of 10 to 40 µg nightly), oral tablets, and a rapidly melting oral lyophilisate (both administered in doses of 100 to 400 µg nightly). It is logical to assume that the reason for antidiuretic effect of desmopressin is reduced urine production [1-4]. There is, however, also some evidence that central nervous system effects may be active as well [2-4].

Desmopressin is generally considered a safe drug for enuresis and has been prescribed in many millions of cases [1-4]. The purpose of our systematic review of the literature was not to provide an overview of desmopressin tolerability, but rather to investigate the very rare cases that present with severe symptoms of hyponatremia secondary to desmopressin treatment for

enuresis. In enuresis managed with desmopressin, dilutional hyponatremia may develop following excess fluid intake, during intercurrent illnesses that might otherwise affect fluid balance or in case of prolonged desmopressin bioactivity [43]. The present report indicates that excessive fluid intake and intercurrent clinical illnesses that might otherwise affect fluid balance very often precede severe hyponatremic encephalopathy in subjects with enuresis on either nasal or oral desmopressin. An increased bioactivity of desmopressin can be caused by an excessive absorption through the nasal mucosa, since both allergic and inflamed airways significantly change the bioavailability of nasally administered desmopressin [2-4, 43]. Finally, a prolonged duration of action with conventional doses of intranasal desmopressin has been documented in a small group of enuretic subjects [30].

More than 85 percent of the reported subjects who developed severe hyponatremic encephalopathy were on nasal desmopressin, suggesting that the oral formulation is safer [44]. An alternative possibility to account for the smaller number of case reports with the oral formulation is that the medical community has presumed that the literature contains a sufficient number of case reports of hyponatremia associated with nasal desmopressin (prescribed for enuresis since approximately 1980) management and the occurrence with an oral formulation (prescribed since 1990) is no longer reportable. Another possibility is that the oral formulations have been marketed for a shorter period. Notwithstanding these possibilities, it is assumed that the oral application harbors a safety profile superior to the intranasal route [2-4, 44]. In the present analysis, blood sodium was significantly lower in patients treated with intranasal desmopressin, further supporting the mentioned assumption. We think that administration of a higher than recommended dose is more likely with an intranasal formulation: some patients might feel unsure whether an adequate dose has been administered with an intranasal formulation and they might increase the dose to compensate for this uncertainty [2-4, 44]. In fact, desmopressin intranasal formulations are

no longer indicated for the treatment of enuresis. Furthermore, considering that young age was identified as a risk factor for hyponatremia, desmopressin is not recommended for enuretic children younger than 6 years [2-4, 44].

Conclusions

Severe hyponatremic encephalopathy is a very rare but recognized complication of management with desmopressin in subjects affected by enuresis. This complication mostly develops 14 days or less after starting the medication, following excess fluid intake, during intercurrent illnesses and in subjects managed with the intranasal formulation. It is often preceded by headache, nausea or vomiting that appear the morning and by a delayed first morning voiding following desmopressin administration in the evening.

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Figure 1- Legend

Flowchart of the literature search process.

Table 1: Clinical and laboratory data in subjects with severe signs of hyponatremia secondary to desmopressin treatment for enuresis.

	All cases	Severely Altered Mental Status	Convulsions	Significance
N	54	8	46	
Desmopressin, nasal/oral	47/7	5/3	42/4	Not significant
Gender, male/female	34/20	2/6	32/14	P<0.05
Age, years	9.0 [6.5-11]	9.0 [7.8-19]	9.0 [6.0-11]	Not significant
Age ≤6.0 years, N	11	1	10	Not significant
Blood sodium level, mmol/L	119 [116-122]	124 [120-125]	118 [115-121]	P<0.01
Contributing factor				
Excess fluid intake, N	25	4	21	
Intercurrent illness, N	6	1	5	
Total, N	31	5	26	Not significant

The results are given either as median (with interquartile range between brackets) or as relative frequency.

Table 2: Clinical and laboratory data in subjects with severe signs of hyponatremia secondary to either nasal or oral desmopressin treatment for enuresis.

	Oral Desmopressin	Nasal Desmopressin	Significance
N	7	47	
Age, years	9.0 [6.5-10]	9.4 [6.5-12]	Not significant
Gender, male/female	4/3	30/17	Not significant
Altered mental status/convulsions	3/4	5/42	
Blood sodium level, mmol/L	124 [122-126]	116 [118-121]	P<0.02
Contributing factors			
Excess fluid intake, N	5	25	
Intercurrent illness, N	1	5	
Total, N	6	30	Not significant

The results are given either as median (with interquartile range between brackets) or as relative frequency.